SECTION II

MECHANISM OF ACTION

CHAPTER 5

THE EFFECTS OF LISINOPRIL ON RENAL HEMODYNAMICS IN PATIENTS WITH RENAL DISEASE

Jan E. Heeg, Dick de Zeeuw, and Paul E. de Jong

Current Opinion in Cardiology 1989;4(suppl 1):29-34

ABSTRACT

The effects of lisinopril on renal hemodynamics in patients with renal disease.

Although the effects of angiotensin converting enzyme (ACE) inhibition on renal hemodynamics are fairly well documented in normal subjects and in patients with essential and renovascular hypertension, less is known about the renal effects of ACE inhibitors in patients with renal disease. The few reports mention either a fall or a rise in glomerular filtration rate (GFR). We studied the renal hemodynamic effects of different doses of the ACE inhibitor lisinopril in different conditions of volume status in patients with renal disease, either with or without hypertension. In all situations, filtration fraction and renal vascular resistance fell, like in patients with normal renal function. In contrast to patients without renal disease, in our patients GFR often decreased during ACE inhibition, mostly in parallel with the fall in systemic blood pressure. However, when the renal effects of lisinopril were studied while blood pressure was kept stable in the comparison with control study periods, there was no fall in GFR. The GFR fell only when the dose of the ACE inhibitor was increased and blood pressure was further lowered. The GFR lowering effect of the ACE inhibitor in these patients appeared to be strictly dependent on the degree of volume depletion, since substituting a low for a high sodium diet abolished the fall in GFR. These data show that ACE inhibitors can induce a decrease in the GFR in patients with renal disease. This occurs particularly in case of substantial blood pressure reduction and can be attenuated by reducing the dose of the ACE inhibitor or by volume repletion.

INTRODUCTION

Angiotensin converting enzyme (ACE) inhibitors have distinct renal effects. Generally, the glomerular filtration rate (GFR) remains stable notwithstanding the concomitant fall in systemic blood pressure [1-4]. This maintenance of GFR can be explained by the rise in effective renal plasma flow (ERPF). The characteristic profile of ACE inhibitor-induced changes in renal function is therefore a fall in filtration fraction [1-4]. This fall is interpreted as a predominantly efferent vasodilation [5]. Indeed, efferent vascular tone is determined to a large extent by angiotensin II [6], and blockade of the renin-angiotensin system will thus induce a fall in postglomerular vascular tone. This renal response to ACE inhibition, both in normal subjects and in patients with hypertension, is in contrast with the changes in renal function that can occur in patients with renovascular hypertension. Different reports have mentioned a reversible fall in the GFR after ACE inhibition in renovascular hypertension [7-10].

Although the effects of ACE inhibition on renal function in essential hypertension and renovascular hypertension are well documented, less is known about these effects in patients with renal disease. Some reports have described reversible renal failure during ACE inhibition [11-14], but other studies have reported a stable GFR [15, 16] or even an improvement in renal function during ACE inhibition [17, 18]. We now report three prospective studies on the effects of ACE inhibition in patients with renal parenchymal diseases of various origins. Patients with and without hypertension were studied. Particular attention was given to the dose dependency of changes in renal function, the relation between the changes in blood pressure and the concomitant changes in renal function, as well as the role of the pre-existing volume balance.

PATIENTS AND METHODS

To evaluate the effects of lisinopril on renal hemodynamics in patients with renal disease, three different studies were performed.

Lisinopril in renal disease with hypertension

Changes in hemodynamics during lisinopril therapy were studied in patients with hypertension and renal failure (GFR 10-60 ml/min). Nine patients from a group of 16 subjects described elsewhere [19] were included in this analysis. The primary goal of the treatment with lisinopril in these patients was to reduce blood pressure. These nine patients were selected because they were treated with lisinopril as monotherapy and renal hemodynamics were studied for at least 6 months. Mean $\pm$ SD age was 48 ± 8 years; two were females and seven were males. The renal diseases were polycystic kidney disease ($N = 2$), chronic pyelonephritis ($N = 1$), membranoproliferative glomerulonephritis ($N = 1$), local focal glomerulosclerosis ($N = 2$),

Wegener's granulomatosus ($N = 1$), and atherosclerosis with ischemia ($N = 2$). Six patients had proteinuria with a mean 24-hour urinary protein loss of 2.5 ± 1.0 g. The patients were followed in our outpatient nephrology unit and were treated with conventional antihypertensive drugs before the start of this study. Previous antihypertensive therapy was withdrawn at least 2 weeks before the lisinopril was started. They were maintained on a dietary regimen of 50-70 mmol sodium chloride per day. A protein intake of 30-40 g/day had been advised for patients with a GFR of less than 30 ml/min, and 40-60 g/day for patients with a GFR of 30-60 ml/min.

Lisinopril was titrated gradually in 2-week intervals. Patients with an initial GFR of less than 30 ml/min started with a dose of 2.5 mg, and those with a GFR of more than 30 ml/min started with 5 mg lisinopril per day. If the therapeutic goal was not reached after 2 weeks, the dose was doubled, in some patients up to a maximum of 40 mg per day. In this patient group the therapeutic goal was reached on lisinopril monotherapy within a 3-month period. Since the GFR appeared to be decreased at that time, we then tried to lower the lisinopril dose gradually during the next 3 months. The GFR, ERPF, and urinary sodium and protein excretion were measured the day before the first lisinopril dose, after titration (at 3 months) and after 6 months of treatment.

Lisinopril in renal disease without hypertension

In this study the effects of lisinopril on renal hemodynamics were studied in patients with renal disease and normal blood pressure. The eight patients included in this analysis belonged to a group of 10 patients described previously in a study on the antiproteinuric effects of lisinopril [20]. The causes of the renal diseases were membranous glomerulopathy ($N = 4$), glomerulosclerosis ($N = 2$), and local focal glomerulonephritis and non-steroid-sensitive minimal-change disease in one patient. Mean age was 38 ± 12 year; four female and four male patients were included.

The patients had a mean pretreatment blood pressure of 130 ± 12 mmHg systolic and 79 ± 10 mmHg diastolic, a GFR of 79 ± 26 ml/min and proteinuria of 5.4 ± 1.5 g/day with serum albumin of 34 ± 6 g/l. They were followed in our out-patient nephrology unit, and most of them had been previously treated with a diuretic and a non-steroidal anti-inflammatory drug as antiproteinuric therapy. None had taken steroid or immunosuppressive drug therapy. All therapy was withdrawn at least 2 weeks before this study, and a dietary intake of 50 mmol sodium chloride per day was prescribed. In patients with a GFR of less than 60 ml/min a dietary protein restriction of 60 g per day was prescribed.

In an attempt to study the effects of the ACE inhibitor on renal hemodynamics without interference from the antihypertensive properties of the drug, these normotensive patients were given the antihypertensive drug α-methyldopa in the control period. After a stable period on this regimen (generally 2 months), the α-methyldopa was withdrawn, and the dose of lisinopril was titrated to obtain a similar antihypertensive effect. After two months, the dose of lisinopril was doubled

in all patients. Similar studies to those mentioned above were performed at the end of the α-methyldopa period and after a 2-months period on the low and on the higher dose of lisinopril.

Lisinopril under different conditions of sodium balance

The influence of changes in salt intake on the renal hemodynamic effects of lisinopril was studied in a subset of the 10 patients referred to in the second of the present studies. Eight patients (two females and six males) with a mean age of 43±12 years, were included. The renal disease was caused by membranous glomerulopathy in 6 patients, and by glomerulosclerosis and local focal glomerulonephritis in one patient. Initial systolic blood pressure was 134±14 mmHg and diastolic blood pressure was 89±11 mmHg. The GFR was 72±23 ml/min, and 24-hour urinary protein loss was 6.5±2.5 g. As described above, the patients were first studied during a 2-month period on α-methyldopa, followed by the lisinopril period (mean dose 10±4.3 mg). A sodium intake of 50 mmol per day was prescribed. Thereafter, the sodium content of the diet was changed to a 200 mmol intake per day, while the dose of the ACE inhibitor was kept constant. Renal function and electrolyte studies were carried out at the end of the α-methyldopa period and after a 2-month period of lisinopril on the low-salt diet and a 2-month period on the high-salt diet.

METHODS

Blood pressure was measured at 1-minute intervals by a Dinamap^{R} recorder after 10 minutes of supine rest. The mean value of at least five readings was recorded. Urinary protein was analysed by a biuret method. The GFR and ERPF were measured by constant infusion of ^{125}I-iothalamate and ^{131}I-hippuran, respectively. Both were corrected for standard body surface area (1.73 m^2). The coefficients of variation were 2.2% and 5.0%, respectively [21]. The filtration fraction was calculated as the quotient of GFR and ERPF. Renal vascular resistance was calculated as the ratio of mean arterial blood pressure to ERPF.

Statistical analysis was performed with Wilcoxon's test for paired data. Unless otherwise indicated, means ± SD are given. $P < 0.05$ was considered significant.

RESULTS

Lisinopril in renal disease with hypertension

The mean dose of lisinopril used was 19±14 mg/day after 3 months and 13±13 mg/day after 6 months of treatment. Both systolic and diastolic blood pressures were lower after 3 months of treatment ($P < 0.01$; *Figure 1*). When the lisinopril dose was reduced during the next 3 months, diastolic blood pressure did not change significantly, although systolic blood pressure increased slightly ($P < 0.01$). Both systolic and diastolic blood pressure remained significantly lower compared to

pretreatment values. Changes in renal hemodynamics during these different periods are also given in *Figure 1*. The ERPF showed a 10±13% rise (NS) initially and remained stable thereafter. In contrast, GFR fell by 19±11% during the first 3 months ($P < 0.01$), but increased again during the following 3-month period ($P < 0.05$). The filtration fraction fell by 25±7%, from 0.27±0.04 to 0.20±0.03 ($P < 0.01$) after 3 months of therapy, and rose slightly after 6 months of therapy to 0.24±0.04 ($P < 0.02$), but remained significantly lower than the control value. Similarly, renal vascular resistance fell from an initial 1.08±0.39 to 0.77±0.31 mmHg/ml per min ($P < 0.02$) after 3 months, and 0.82±0.32 mmHg/ml per min ($P < 0.02$) after 6 months of treatment. In the six proteinuric patients, urinary protein excretion decreased from 2.5±1.0 g/day to 0.4±0.7 g/day after 3 months ($P < 0.05$), and 0.7±0.9 g/day ($P < 0.05$) after 6 months of lisinopril.

Lisinopril in renal disease without hypertension

In the second study we evaluated the decrease in the GFR during ACE inhibition in renal disease, in order to determine whether it was dose dependent and/or depen-

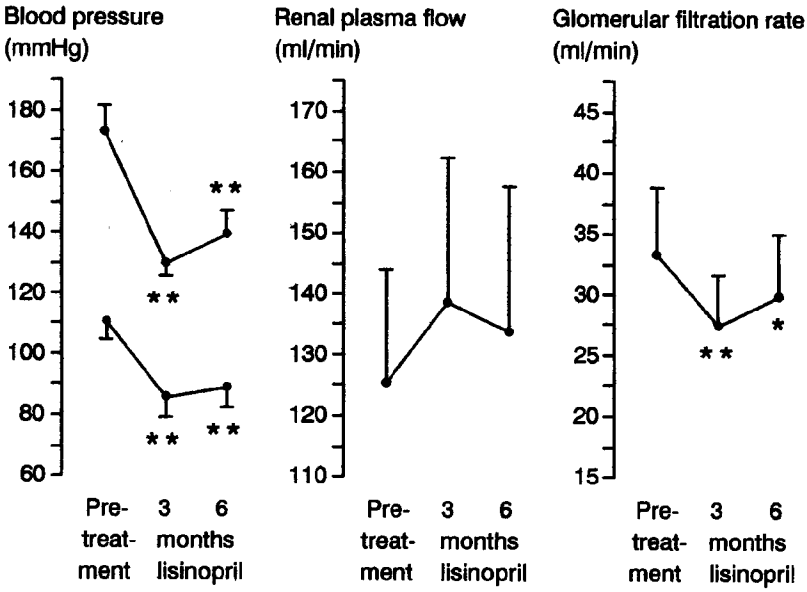

Figure 1:
*The effects of 3 and 6 months treatment with lisinopril on blood pressure, effective renal plasma flow and glomerular filtration rate compared to a pretreatment period without antihypertensive therapy in 9 patients with renal disease and hypertension. Means and SEM are given; * = $P < 0.05$ and ** = $P < 0.01$ compared to the pretreatment values.*

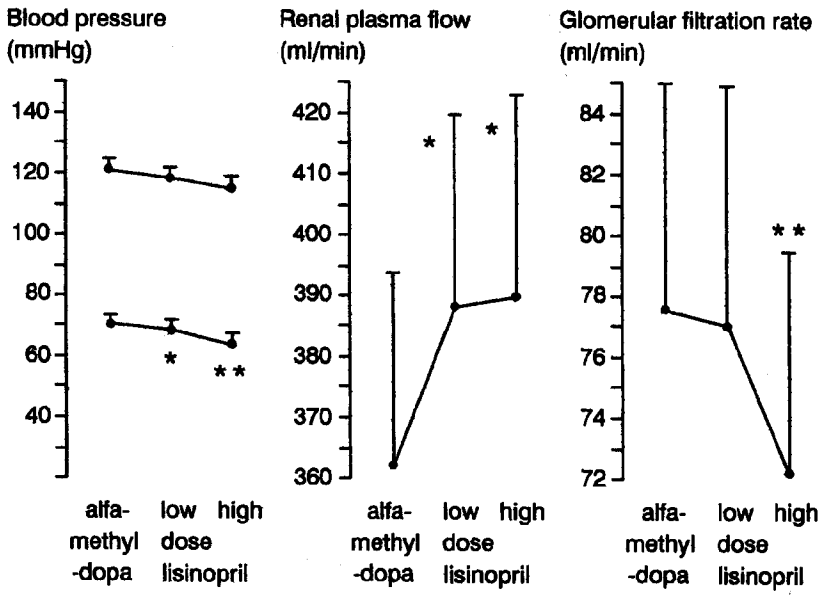

Figure 2:
The effects of two different doses of lisinopril on blood pressure, effective renal plasma flow and glomerular filtration rate compared to antihypertensive therapy with α-methyldopa in eight patients with renal disease and normal blood pressure. Means and SEM are given; * = $P < 0.05$ *and* ** = $P < 0.01$ *compared to the values during α-methyldopa.*

dent on concomitant changes in blood pressure. The effects of the low and the higher doses of lisinopril were therefore compared with measurements made after arterial blood pressure was lowered by α-methyldopa to 121±12/70±8 mmHg. Blood pressure and renal hemodynamic data during treatment with α-methyldopa and lisinopril are given in *Figure 2*. The mean doses of lisinopril were 4.4±1.1 (low dose) and 9.4±1.7 mg/day (higher dose). Although systolic blood pressure did not differ during the treatment with low dose lisinopril compared with α-methyldopa, diastolic blood pressure was 3.3±3.9% lower ($P < 0.05$) during lisinopril. There was a 7.8±10.0% rise in ERPF ($P < 0.05$), but the GFR remained stable during the low dose of lisinopril. Only after the dose of lisinopril was increased did the GFR fall, by 6.6±3.2% ($P < 0.01$ versus α-methyldopa), in parallel with a 7.9± 4.6% decrease ($P < 0.01$) in diastolic blood pressure. The fall in GFR occurred notwithstanding a stable ERPF. The filtration fraction (initially 0.22±0.04) decreased to 0.20±0.04 (NS) during the low-dose treatment, but fell further on the higher dose of lisinopril to 0.19±0.03 ($P < 0.01$ versus α-methyldopa). Renal vascular resistance (initially 0.26±0.08 mmHg/ml per min) decreased to 0.23±0.08

mmHg/ml per min ($P < 0.05$) during low dose as well as higher dose lisinopril treatment. Proteinuria fell from 6.0±1.8 g/day during treatment with α-methyldopa to 4.9±1.8 g/day ($P < 0.01$) on low dose lisinopril and to 3.1±1.1 g/day ($P < 0.01$) on the higher dose of lisinopril.

Lisinopril under different conditions of sodium balance

To further evaluate the renal effects of ACE inhibition, we carried out a study to determine whether these effects are dependent on sodium balance. After treatment with α-methyldopa and with lisinopril on a low sodium diet, the patients were maintained on a high sodium diet during the following period, while the lisinopril treatment was continued. Twenty-four hour urinary sodium excretion in the 3 periods was 89±38, 74±11 and 181±32 mmol, respectively. Corresponding body weights were 79.9± 10.3, 78.7±10.3, and 80.4±10.7 kg. Body weight was lower during lisinopril compared with α-methyldopa treatment ($P < 0.01$), but increased again during the higher sodium intake ($P < 0.01$). Data on blood pressure and renal hemodynamics are given in *Figure 3*. Both systolic and diastolic blood pressures were lower during lisinopril treatment in the salt-depleted condition ($P < 0.05$). ERPF increased by 4.1±6.2% (NS) and GFR fell by 7.2±4.5% ($P < 0.01$). After the sodium intake was increased, blood pressure rose again, reaching the value obtained during α-methyldopa treatment. ERPF increased further (9.9±13.7%, $P < 0.05$ compared with α-methyldopa), and GFR rose to the same value obtained during α-methyldopa treatment. The filtration fraction decreased from 0.21±0.04 to 0.19±0.04 ($P < 0.01$) during lisinopril treatment, with both low and high salt intakes. Similar changes occurred in renal vascular resistance. Proteinuria fell from 6.5±2.1 g/day during α-methyldopa to 3.3±1.3 g/day during lisinopril treatment with low salt intake ($P < 0.01$), but returned to the baseline values during lisinopril therapy with the high salt diet (6.2±3.1 g/day).

DISCUSSION

We have shown that ACE inhibition clearly influences renal function in patients with renal disease. Although the filtration fraction and renal vascular resistance consistently decreased during ACE inhibition in these patients, the effect on the GFR was quite different compared with the known effects of ACE inhibition in patients without renal disease. In the latter the GFR is nearly always stable or even increasing [1-4]; we have shown that the GFR can decrease in patients with renal disease, both with and without hypertension. These effects on GFR, however, do not always occur. They are particularly evident in cases of a marked fall in blood pressure and can be attenuated either by lowering the dose of the ACE inhibitor or by volume repletion.

How can these differences in renal response to ACE inhibitors be explained? Studying the role of the renin-angiotensin system in the normal kidney can throw

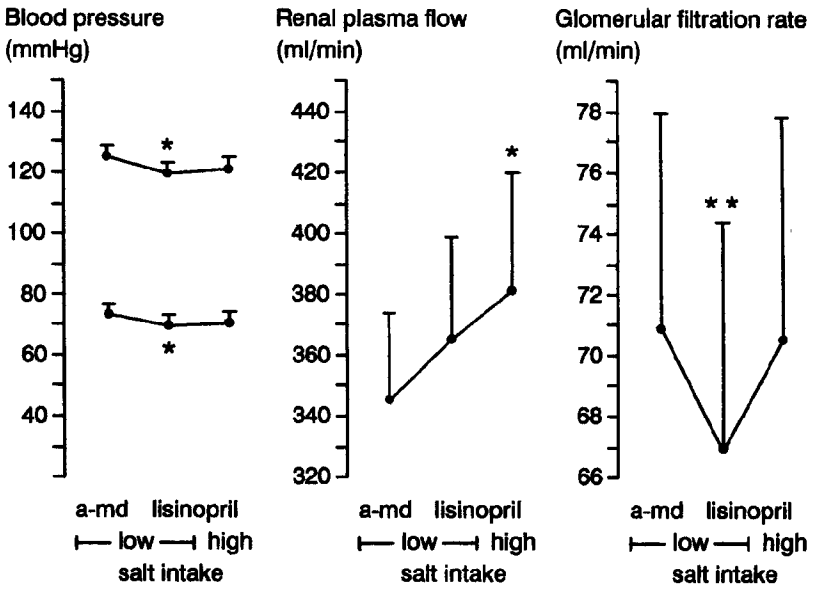

Figure 3:
*The influence of changes in salt intake on the effects of lisinopril on blood pressure, effective renal plasma flow and glomerular filtration rate compared to α-methyldopa (a-md) in eight patients with renal disease. Means and SEM are given; * = $P < 0.05$ and ** = $P < 0.01$ compared to the values during α-methyldopa.*

some light on this issue. Under normal conditions the kidney is able to maintain normal filtration within a wide range of renal perfusion pressures (so-called renal autoregulation), due to constriction of the efferent arteriole during a fall in perfusion pressure. Constriction of the efferent arteriole is largely dependent on the activity of the renin-angiotensin system. With diminished arterial blood flow to the kidney, as in the case of a renal artery stenosis but also in renal function impairment or depletion of the effective circulating volume such as in case of severe heart failure, maintenance of the GFR is particularly dependent on the normal functioning of the renin-angiotensin system. The balance between perfusion pressure and adequate glomerular filtration then becomes highly delicate. Under these circumstances, ACE inhibitor therapy can alter this balance so that adequate glomerular filtration can no longer be maintained [5, 22]. The reports of a fall in the GFR after ACE inhibition in renovascular hypertension should be interpreted in this context [7-10]. However, it has been shown that an ACE inhibitor-induced fall in glomerular filtration in patients with a renal artery stenosis is reversible after withdrawal of the ACE inhibitor [7-10]. The deleterious effect of ACE inhibition on the GFR in such

patients can also be attenuated by volume repletion [23, 24]. This demonstrates the intricate balance between volume homeostasis, the renin-angiotensin system, and renal function.

A fall in the GFR coincident with a fall in systemic blood pressure in our patients with renal disease could well reflect that in these patients maintenance of glomerular filtration is also strictly dependent on adequate efferent vasoconstriction. In the presence of a blockade of the renin-angiotensin system, renal autoregulatory capacity fails, and a fall in blood pressure will induce a decrease in the GFR, as has been shown in renovascular hypertension. And, like in patients with renal artery stenosis, we were able to show that this effect on the GFR in patients with renal disease can also be modulated.

The first of the present studies suggested that it was possible to attenuate the GFR lowering effect of the ACE inhibitor in patients with renal disease by lowering the dose of the drug. This was accomplished without loss of antihypertensive potency. Although systolic blood pressure increased, it remained well within acceptable limits. This shows that physicians should titrate an ACE inhibitor carefully in patients with renal failure. Often very low doses will supply adequate blood pressure control. However, this first study was unable to show whether the fall in GFR during lisinopril treatment was the consequence of the blood pressure reduction itself, or whether it is a characteristic of ACE inhibition.

We therefore carried out a second study to determine whether lisinopril induces a fall in the GFR when the blood pressure remains unchanged. Although the renal function impairment of the patients included in this second study was not as great as that described in the first study, it is clear from *Figure 2* that the GFR remained stable and that ERPF increased during lisinopril treatment in comparison with controls whose blood pressure values were comparable. However, after the dose of the ACE inhibitor was doubled to obtain a better antiproteinuric effect, the GFR did fall, with a parallel decrease in blood pressure, notwithstanding a stable elevation in ERPF. Since these patients complied adequtely with the dietary salt restriction, the renin-angiotensin system was stimulated, and, as already described, blockade of this system in association with a reduction in blood pressure endangered the GFR.

The relevance of sodium balance to the effects of ACE inhibitors on renal function is further supported by the data from the third of the present studies. When sodium intake was increased, giving an apparently positive sodium balance (body weight increased), while the ACE inhibitor therapy was unchanged, the fall in GFR was virtually abolished and ERPF increased further. These data are strikingly similar to the findings in patients with renovascular hypertension. As mentioned before, volume repletion can attenuate the potentially harmful effect of ACE inhibitors on renal function in patients with renal artery stenosis [23, 24]. We showed that this also appears to be true for the ACE inhibitor-induced fall in the GFR in patients with renal disease.

We conclude that lisinopril can induce a fall in GFR in patients with renal disease, either with or without hypertension. This fall in GFR can be corrected either by lowering the dose of the drug or by volume repletion. These data stress the importance of careful dose titration together with monitoring of renal function if ACE inhibitors are prescribed to patients with renal disease.

ACKNOWLEDGEMENTS

These studies were performed in the Department of Nephrology, State University Hospital Groningen, the Netherlands, and were supported by Grants No 82-372 and 87-691 from the Dutch Kidney Foundation (Nier Stichting Nederland). We are much obliged to Mrs. A. Drent-Bremer, who performed the renal function studies, and to Mrs. P.T. Hesling-Kuiper for technical and secretarial assistance.

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